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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/755,633	01/05/2001	Shumin Yang	IM-2-C1-C1	4819

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EXAMINER
KAUSHAL, SUMESH

ART UNIT	PAPER NUMBER
1636	9

DATE MAILED: 03/31/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/755,633	YANG ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5,6
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other

DETAILED ACTION

Applicant's response filed on 01/14/03 has been acknowledged.

Election/Restrictions

In response to applicant arguments filed on Paper No:8 the restriction requirement issued on 12/17/02 has been withdrawn.

Claims 1-18 are pending and are examined in this office action.

► *Applicants are advised to follow Amendment Practice under revised 37 CFR §1.121 (http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/revamdtprac.htm). Each amendment document that includes a change to an existing claim, or submission of a new claim,* ***must include a complete listing of all claims*** *in the application. After each claim number, the status must be indicated in a parenthetical expression, and the text of each claim under examination (with markings to show current changes) must be presented. The listing will serve to replace all prior versions of the claims in the application.*

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1, 3, 5-11, 13-14 and 17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

[illegible] had possession of the claimed invention

The scope of invention as claimed encompasses any and all variants or homologs of SEQ ID NO:18 and SEQ ID NO:19, wherein at least a 45 consecutive nucleotide region is identical to a 45 contiguous nucleotide region of SEQ ID NO:18 and SEQ ID NO:19, but the 45 contiguous nucleotide region is NOT found in SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9 or SEQ ID NO:11 (see claim limitation). Furthermore, the scope of invention as claimed also encompasses isolated nucleic acid sequences that is at least 90% identical to SEQ ID NO:18 or 19. The scope of invention as claimed also encompasses any and all allelic variants of nucleic acid encoding the amino acid of SEQ ID NO: 5 and 10. The scope of invention as claimed also encompasses a therapeutic composition and a method to regulate immune response in an animal by administering the nucleic acid as described above. In addition the scope of invention as claimed encompasses any and all natural and non-natural variant of SEQ ID NO:18 and 19 wherein the nucleic acid is obtained from any and all organisms (other than dog).

Applicant is referred to the Interim guidelines on *Written Description* published December 21, 1999 in the Federal Register, Vol. 64, No. 244, pp. 71427-71440. The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). At best the instant specification as filed teaches the nucleic acid sequence of SEQ ID NO: 18 and 19 (reverse complement of SEQ ID NO:18) which encodes the amino acid sequences of SEQ ID NO:5 and 10 (Canine IL-5). The specification fails of disclose any variants of nucleic acid sequence of SEQ ID NO: 18 and 19 or nucleic acid encoding the amino acid of SEQ ID NO: 5 and 10 that has any IL-5 like activity explicitly or implicitly as putatively considered by the instant specification. The specification fails to define the minimal structure or consensus core structure that defines the genus comprising nucleotide sequences encoding the amino acid sequences of IL-5. The possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person

(1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical,

927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). In claims to genetic material, generic statement such as "vertebrate insulin cDNA" or mammalian insulin cDNA," without more, is not adequate written description of claimed genus, since it does not distinguish genus from others except by function, and does not specifically define any of genes that fall within its definition, or describe structural features commonly possessed by members of genus that distinguish them from others; accordingly, naming type of material generally known to exist, in absence of knowledge as to what that material consists of, is not description of that material (*Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406).* In the instant case the nucleic acid variants (as claimed) has been defined only by a statement of function that broadly encompasses regulation of any and all components of immune response (humoral or cellular) in any and all animals (insect, reptiles, amphibians, birds and mammal etc), which conveyed no distinguishing information about the identity of the claimed DNA sequence, such as its relevant structural or physical characteristics. The variation as claimed also encompasses the conserved motifs, which are considered germane to the functional activity of an IL-5 like polypeptide. For example 10% variation (90% identical) as claimed would certainly affect proper folding and biological activity if amino acids that are critical for such functions are substituted, since the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. Furthermore, mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues (see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976). Furthermore, the scope of invention as claimed encompasses any variant that does NOT even comprise the conserved amino acid sequences required for the IL-5 activity (see claims 1, 11, 14 and 17). Furthermore, considering the scope variants as discussed above it is unclear how one skill in the art would envision an oligonucleotide, recombinant molecule, virus or a cell that comprises the variants as

possession of the claimed genus requires description [illegible] not representative of the variants of genus and is insufficient to support the claim.

2. Claims 1-10 and 17-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated nucleic acid sequences of SEQ ID NO:18 and 19 which encodes the amino acid sequences of SEQ ID NO:5 or 7, and method of producing the same, wherein the recombinant protein has Canine IL-5 activity, does not reasonably provide enablement for any and all natural or non natural variants of SEQ ID NO:18 and 19 obtained from any and all organisms. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature Of Invention:

The invention relates to nucleic acid encoding the Canine IL-5 polypeptide

Breadth Of Claims And Guidance Provided By The Inventor:

The scope of invention as claimed encompasses any and all homologs of SEQ ID NO:18 and SEQ ID NO:19, wherein at least a 45 consecutive nucleotide region is identical to a 45 contiguous nucleotide region of SEQ ID NO:18 and SEQ ID NO:19, but the 45 contiguous nucleotide region is NOT found in SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9 or SEQ ID NO:11. The scope of invention as claimed encompasses isolated nucleic acid sequences that is at least 90% identical to SEQ ID NO:18 or 19. The scope of invention as claimed also encompasses any and all allelic variants of nucleic acid encoding the amino acid of SEQ ID NO: 5 and 10. In addition the scope of invention as claimed encompasses method of producing the variants (as claimed) by culturing a cell capable of expressing the polypeptides encoded by claimed nucleic acid variants. At best the instant specification as filed teaches the nucleic acid sequence of SEQ ID NO: 18 and 19 (reverse complement of SEQ ID NO:18) which encodes the amino acid sequences of SEQ ID NO:5 and 10 (canine IL-5).

State Of Art And Predictability:

The state of the interleukin art at the time of filing teaches that the role of IL-5 in the growth, activation, and survival of eosinophils is complex. IL-5 activates Lyn, Syk, and JAK2 [illegible] (Adachi et al Am J Physiol Cell Physiol 275: C623-C633, 1998). The specification as filed fails

to disclose any variants of SEQ ID NO: 18 or 19 that encodes a polypeptide having IL-5 like activity explicitly or implicitly as putatively considered by the specification. The applicant propose to discover any variant of SEQ ID NO:18 or 19 by identifying at least 45 consecutive nucleotide sequences with a proviso that these 45 nucleotides are NOT present in the coding region (SEQ ID NO: 4, 6, 7, 8, 9 and 11). This renders the invention as claimed unpredictable, since applicant wish to identify a variant that does NOT even comprises the conserved amino acid sequences required for the IL-5 activity. Similarly, the invention as claimed encompass a polynucleotide, which encodes a canine IL-5 like polypeptide wherein 10% of amino acid sequences are added, deleted or substituted over the entire length of the polypeptide (see claim 10). The variation also encompasses the conserved motifs that are germane to the IL-5 activity. At best the specification only discloses the nucleic acid encoding SEQ ID NO:5 having IL-5 like activity but fails to disclose a single variants and/or homolog of SEQ ID NO:18 or 19 that have IL-5 like activity. The specification as filed fails to identify the functional attributes of individual variants other than SEQ ID NO: 18 and 19. It is general knowledge in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. The variants as claimed are only hypothetical proteins because no biological function has been established. The mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues. see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976).

Quantity Of Experimentation Required:

The scope of the claims must bear a reasonable correlation with the scope of enablement

[illegible] in the disclosed SEQ ID NO:18 or 19 is not considered routine. Making and testing a point

mutation is significantly different from the making and testing an amino acid sequences wherein at least 10% amino acids are added, deleted and/or substituted. The number of possible scenario increase geometrically with increase in percent non-identity. Such making and testing is nothing more than an invitation to further experimentation, since the specification can not be relied on to teach how to make the variants as claimed. One has to engage in extensive making and testing in order to obtain variants that meet the requirements for the claimed telomerase activity. This is not considered routine in the art and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed. Therefore, the applicant has not presented enablement commensurate in scope with the claims.

3. Claims 11-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention*.

Nature Of Invention:

The invention relates to composition and a method encompassing gene-based therapeutics.

Breadth Of Claims And Guidance Provided By The Inventor:

The scope of invention as claimed encompasses a composition and method to regulate any and all components of immune response in any and all animals by administering any and all variants or homologs of SEQ ID NO:18 and SEQ ID NO:19, wherein at least a 45 consecutive

[illegible] contiguous nucleotide region [illegible] found in SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9 or SEQ ID NO:11. At best the instant

specification as filed teaches the nucleic acid sequence of SEQ ID NO: 18 and 19 (reverse complement of SEQ ID NO:18) which encodes the amino acid sequences of SEQ ID NO:5 and 10. The specification fails to disclose any composition and method wherein administration of nucleic acid sequences comprising any and all variants of nucleic acid sequences of SEQ ID NO:18 or 19 (in any and all viral or non viral vectors), when administered via any and all routes of administration (systemic or local) in any and all animals results in the regulation of any and all components of immune response (humoral or cellular).

State Of Art And Predictability:

The gene-based therapies are considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. No cures can as yet be attributed to gene therapy. (Rosenberg et al, Science 287:1751, 2000, Verma, Mol. Ther. 1: 493, 2000, Friedmann, Science 287(5461):2163-5, 2000, Anderson WF, Nature 392:25-30, 1998; Verma et al Nature 389:239-242, 1997, Touchette, Nat. Med. 2(1) 7-8, 1996). None of the human studies to date has shown definite efficacy, despite more than 300 protocols involving 3000 patients since September 1990 (Anderson page 25 col.1 para.1). Most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect (Touchette, page 7 col.3, para.1; Anderson page 29 col.1, para.6). Furthermore, Recombinant DNA Advisory committee (RAC) also emphasized that expectations of current gene therapy protocols have been over sold without any apparent success (Touchette page 7, col.1 para. 2; page 8, col.2 para 1-4). The advisory panel further emphasized the need for a greater understanding of an underlying mechanism that contribute to a genetic disease along with the pathogenesis of the disease. (Touchette, page 7, col.3, para.3). In instant case the applicant has propose to regulate an any and all component of immune response in any and all animals by administering any and all variants of the nucleic acid sequences encoding the SEQ ID NO:18. The specification fails to disclose a single working example wherein the administration of any variant of nucleic acid (as claimed) would regulate any component of immune system for the

[illegible] encoded by polynucleotides variants (as claimed).

Furthermore, it has been difficult to predict the efficiency and out come of transduced therapeutic genes because various factors govern the expression and/or therapeutic potential of transduced genes in vivo. The transduction of target cells represents the first critical step in gene therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors (Verma et al, see page 239 col.3 par.2, page 242, table-2). Furthermore, in vitro gene transfer studies are not predictive of in vivo gene therapy because gene transfer frequency is much higher in-vitro models where most of cells are under going rapid cell division, which is quite not the case in vivo environment. In addition, besides the limitations in gene transfer the problem to selectively target cells in vivo is still one of the most difficult obstacle to overcome. The viral particles binds to many cells they encounter in vivo and therefor would be diluted out before reaching their targets (Anderson WF, page 25 col.2, para.4). Even though, the gene therapy holds much promise to come, the success will only be achieved through continued rigorous research on the most fundamental mechanisms that contribute to a genetic disease along with the pathogenesis of the disease, gene delivery and gene expression in animals

In addition, an infectious disease is the result of distinct pathogenesis induced by a particular pathogen, and depends upon various factors that encompass both host and pathogen structure and functions. The making of naked DNA vaccine requires the serological characterization of a pathogen to identify neutralizing epitopes and the identification of genes coding the required amino acid sequences (Watts et al, Int. J. Parasitology 29:1149-1163, 1999). Even though the specification teaches that the polypeptide encoded by the nucleotide sequences of SEQ ID NO:18 is a Canine IL-5, the specification fails to provide any guidance regarding what is the essential epitopes structure(s) which is considered germane to elicit the required immune response (*scope of invention as claimed requires a variant that lacks coding region*). Even though one skill in the art would be able to generate antibodies against the variants as claimed it is unclear how an antibody raised against such variant would block the canine IL-5 activity.

The state of the cytokine art at the time of filing teaches that the role of IL-5 in growth,

[illegible] JAK2 tyrosine kinases and SHP-2 tyrosine phosphatase are important for eosinophil survival

(Adachi et al Am J Physiol Cell Physiol 275: C623-C633, 1998). In addition IL-5 is also known to a play role in Th2 immune response. However, the regulation and effects of Th2 response in an animal is complex since it requires a cascade of molecular and cellular interactions among Th2-cytokines IL-4, IL-5, IL-9 and IL-13). Th2 cytokine response is involved in immune rejections of parasite helminth infections, allergies and asthma (McKenzie, Pharma. Ther. 88:143-151, 2000). Therefore considering the role of multiple cytokines in Th2 immune response, it is unclear how one skill in the art would use any variants of IL-5 (as claimed) to regulate Th2 immune response. In addition the art at the time of filing clearly teaches that even though IL-5 is a factor that regulate the differentiation and activation of eosinophils, other factors regulating the differentiation, proliferation and activation of canine eosinophils are not fully understood (Yang et al J Interferon Cytokine Res 21(6):361-7, 2001). Thus considering the limited guidance provided in the instant specification it is unclear how one skill in the art would modulate the immune response by administering nucleic acid sequences (as claimed) in any and all animals (other than dogs).

* *In addition the scope of invention as claimed encompasses any and all variants of SEQ ID NO: 18 or 19 that has at least 45 consecutive nucleotide sequences with a condition that these 45 nucleotides are NOT present in the coding region (SEQ ID NO: 4, 6, 7, 8, 9 and 11). This renders the use of claimed variants unpredictable, since applicant wish use any variant that does not comprises the conserved amino acid sequences required for the IL-5 activity* ***(see Sec. 1 and 2 above, regarding polynucleotide variants as claimed).***

Quantity Of Experimentation Required:

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). In instant case regulation of any and all components of immune response (*humoral or cellular*) using any and all variants of SEQ ID NO:18, (wherein the variant does NOT encode the conserved motifs required for Canine IL-5 activity) in any and all animals (other than dog) is not considered routine in the art and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and

[illegible] broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714

(BPAI 1991). Furthermore, it is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson , 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion"*) Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. Therefore, considering the limited guidance provided in the specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed. The undue experimentation require would include making and testing any and all variants of canine IL-5 to modulate any and all component of immune response in any and all animals in context of any and all diseases.

Claim Objections

Claim 4 and 18 are objected to because of the following informalities: The instant claims recites "the nucleic acid molecule nCaIL-5_{1658} ". It is unclear what is nCaIL-5_{1658} in this context. Incorporation of a designated -- SEQ ID NO: -- after nCaIL-5_{1658} has been suggested. Appropriate correction is required.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to [illegible] whose telephone number is [illegible]. The examiner can normally be reached on [illegible] If attempts to reach

the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-8724 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

S. Kaushal
PATENT EXAMINER

SUMESH KAUSHAL
PATENT EXAMINER